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Antimicrobial Profile of Synthesized B-Cyclodextrin-Isatin (Schiff's Bases) Inclusion Complexes

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KEYWORDS

Isatin Schiff base derivatives,β-Cyclodextrin, inclusion complexes, spectroscopic characterization, antimicrobial activity.

ABSTRACT:

Isatin derivatives are vulnerable known motifs by virtue of diversified bioactivities and synthetic applicability. Herein assorted Isatin Schiff's bases as 1-(2-oxoindolin-3-ylidene)thiosemicarbazide (G1) and 3-((4-chlorobenzylidene)hydrazono)indolin-2-one were assembled and characterized for innate potent antimicrobial profile. Moreover, allied inclusion complexes with β-Cyclodextrin were prepared so as to attain augmented pattern of pharmacological profile. Synthesized Isatin derivatives exhibited UV λmax 373nm and 410 nm for G1 and G2 respectively, FT-IR and 1H NMR data that validated Schiff's base formation. β-Cyclodextrin-Isatin (Schiff's bases) inclusion complexes were prepared by co-precipitation method and verified by preliminary physico-chemical examinations such as colour changes, alteration in melting point etc. and further confirmed by spectroscopic techniques like FT-IR and 1H NMR. Antimicrobial profile demonstrated significant bioactivity against bacterial strains, with minimum inhibitory concentrations (MICs) range 10-50 µg/mL. Certain inclusion complexes showed potent bioactivity against Candida albicans, with MICs as low as 20 µg/mL. The fruitful synthesised and characterized Isatin derivatives and allied inclusion complexes with β-CD showed enhanced antimicrobial profile against assorted pathogens like Pseudomonas aeruginosa, Salmonella typhi, Staphylococcus aureus and Candida albicans. These research findings highlighted the worth of Isatin derivatives and allied inclusion complexes as prominent motifs in order to develop significant pharmaceutical formulations, particularly in combating microbial infections and diseases.

1. Introduction

In contemporary chemistry, a prominent domain of exploration revolves around supramolecular chemistry, often referred to as "chemistry beyond the molecules." This discipline delves into the intricate structures formed by two or more distinct molecules, solely united by intermolecular forces (Feihe Huang et al., (2015). This field showcases a plethora of examples, including cyclic peptides, macrocyclic antibiotics, biologically significant ionophores, clays, zeolites, and other natural and synthetic molecules, all contributing to the rich tapestry of supramolecular chemistry. Notably, even naturally occurring carbohydrates exhibit large-sized components that can serve as supramolecular host systems, with cyclic oligosaccharides being among the identified examples. Within this group, cyclodextrins emerge as particularly fascinating constituents, adding depth to the exploration of natural compounds in supramolecular chemistry. Ariga *et al.*,(2006); de la Peña *et al.*,(2000); Pedersen *et al.*, (1988).

Natural cyclodextrins, discovered by Villiers in 1891 and further studied by Schardinger, are enzymatically produced by Bacillus macerans' cyclodextrinase from starch compounds. These cyclodextrins, including α-, β-

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, and γ-CDs, feature toroidal macrocycles with a central cavity, offering structural versatility. Their hydrophobic cavities, lined with protons and glycosidic oxygen atoms, grant them stability under acidic conditions and resistance to acid degradation. While β-CD exhibits low solubility due to hydrogen bonding, all cyclodextrins remain stable under standard conditions. Cyclodextrins interact with various molecules, ions, and radicals through molecular recognition, showcasing chiral recognition capabilities and serving as reliable enzyme models. Typically, in aqueous environments, cyclodextrins encapsulate apolar guest molecules within their cavities, driven by hydrogen bonding and energy release. Various methods are employed for preparing inclusion complexes, each offering distinct advantages. These methods include physical blending, co-precipitation, kneading, co-grinding, microwave irradiation, spray drying, freeze-drying, solution/solvent evaporation, and supercritical antisolvent techniques, facilitating efficient complex formation. Detecting inclusion complexes involves employing a diverse array of spectroscopic and analytical techniques. Optical spectroscopy methods, such as UV-Visible absorption and fluorescence spectroscopy, are adept at revealing alterations in guest molecule properties upon forming complexes with cyclodextrins. Nuclear magnetic resonance (NMR) spectroscopy provides invaluable insights into the molecular structure and dynamics of inclusion complexes, offering a deeper understanding of their behavior. Mass spectrometry techniques, including ESI, FAB-MS, LSIMS, and MALDI-TOF, complemented by conductance measurements and solubility methods, are commonly employed to identify inclusion complexes with precision. Infrared (IR) spectroscopy serves as a powerful tool for detecting interactions between cyclodextrins and guest molecules in solid states, providing crucial information about their binding characteristics. The synthesis and use of inclusion complexes based on Cds in diverse field have been the focus of research over the last few years. AS Al-Abboodi, *et al.,* (2021) investigated the inclusion complex of patchouli alcohol (PA) with β-cyclodextrin to enhance PA's aqueous solubility and stability. Characterization using DSC, FTIR, SEM, and powder X-ray diffraction techniques confirmed the synthesis of the inclusion complex and highlighted its stability and dissolution rate advantages. Krishna Pillai *et al,*. (2017) studied the water solubility of the inclusion complex of albendazole with β-CD for parenteral use in cancer therapy. They also emphasized improving water solubility by synthesizing the inclusion complex with SBE β-CD, demonstrating strong cytotoxic effects on ovarian tumor cells. A. Kulkarni and V. Belgamwar (2017) investigated the in vitro anticancer activity of the inclusion complex of chrysin with sulphobutyl ether-β-cyclodextrin. The complex exhibited significantly higher solubility and dissolution rates compared to free chrysin, resulting in enhanced anticancer activity. Liang Gong *et al.,* (2016) studied the antifungal properties of the inclusion complex of eugenol with β-cyclodextrin. Their in vitro and in vivo studies demonstrated the complex's potential as a controlled-release agent against P. litchi.

In the present studies, attempt has been given to synthesize schiffs bases of Isatin and their inclusion complexes with the supramolecular host β-CD. Spectroscopic methods such as UV, FT-IR, 1H-NMR and mass spectrometry use to verify the synthesis of schiffs bases and inclusion complexes. Antimicrobial assay of guest alone and its inclusion complex were compared.

2. Experimental

2.1 Materials and methods:

All the chemicals are of analytical grades such as Isatin, 1-methyl Isatin, Thiosemicarbazide, Hydrazine hydrate, p-chlorobenzaldehyde, DMSO, and β-cyclodextrin, were obtained by commercial means and used without additional purification. We prepared distilled water in our lab. A Shimadzu Corp. 03093 Fourier transform spectrophotometer was used to obtain FT-IR spectra in KBr in the 400–4000 cm-1 range using the KBr disc method. UV spectra in the 200–780 nm range have been acquired with a UV-2600 Series double-beam spectrophotometer. A spectrophotometer called the BRUKER Avance Neo (1H NMR, 500 MHz) was used to record NMR spectra in CDCl3/DMSO-d6. Values for chemical shift (δ) are given in parts per million.

2.2 General procedure for the synthesis of Isatin Schiff base (G1):

The procedure involves refluxing a mixture comprising 5 mmol of Isatin and 5 mmol of aromatic or heterocyclic primary amines in 50 ml of ethanol, with

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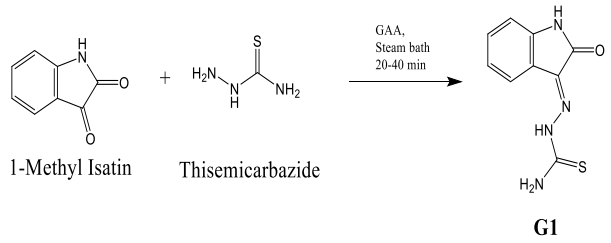
acetic acid serving as the catalyst, typically for a duration ranging from 0.5 to 2 hours. Upon reaching completion, as determined by TLC analysis, the solvent is removed under reduced pressure. Subsequently, the crude product undergoes washing with water followed by recrystallization in ethanol to yield pure products Azizian et al., (2012) (Schemes 1).

2.3 General procedure for the synthesis of Isatin Schiff base (G2):

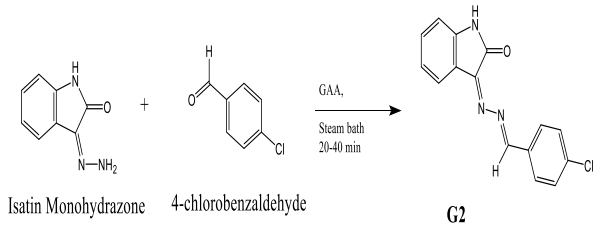
A mixture containing equal amounts (1:1) of Isatin and hydrazine hydrate was subjected to reflux in ethanol, resulting in the quantitative yield of Isatin monohydrazone. Subsequently, the Isatin monohydrazone underwent reflux with p-chloro benzaldehyde in absolute ethanol, with a catalytic amount of glacial acetic acid present, yielding the desired product G5. Al-Salem et al., (2020) (Scheme 2).

2.4 Schemes of the synthesis:

Scheme 1: Synthesis of 1-(2-oxoindolin-3-ylidene)thiosemicarbazide (G1)



Scheme 2: Synthesis of 3-((4-chlorobenzylidene)hydrazono)indolin-2-one (G2)



2.5 Preparation of β-cyclodextrin inclusion complexes:

The preparation of the β-cyclodextrin/Schiff's base (SB) inclusion complex involved employing the co-precipitation technique with a 1:1 ratio. Initially, 1.135 g (1 mmol) of β-cyclodextrin was dissolved in 20 mL of hot deionized water. Following this, 0.241 g (1 mmol) of SB was dissolved in 20 mL of hot ethanol and slowly added to the β-cyclodextrin solution. The resulting mixture was stirred for two hours at room temperature. Afterward, the precipitated complex was separated by filtration to remove any excess SB and β-cyclodextrin, followed by washing with a small amount of ethanol and water. Subsequently, the collected product was dried and stored in airtight containers for future use. Tanwar et al.,(2019)

3. Result and Discussion:

The synthesis of Isatin derivatives (G1 and G2) was achieved through the reaction as shown in the scheme 1 and 2. Comprehensive physical and analytical characterization was conducted to delineate the guest's properties.

The physical characteristics of the Isatin derived schiffs bases are shown in table 1

Table 1: Physical characteristics of the Isatin derived schiffs bases

Isatin Derivatives	Molecular Formula	Melting Point (°C)	% Yeild
G1	C9H8N4SO	198	52
G2	C15H10N3OCl	270	85

3.1 Spectral characterization of 1-(2-oxoindolin-3-ylidene)thiosemicarbazide (G1)

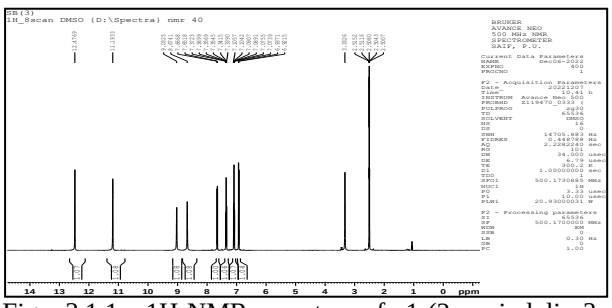


Fig. 3.1.1: 1H-NMR spectra of 1-(2-oxoindolin-3-ylidene)thiosemicarbazide (G1)

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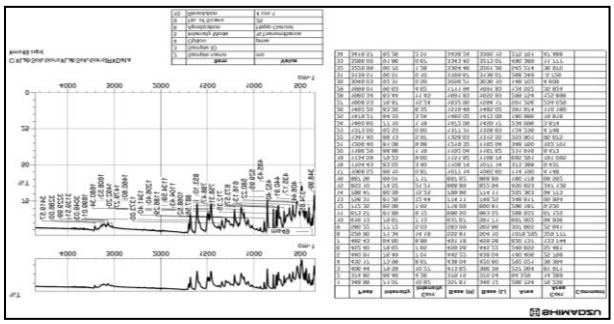

Fig. 3.1.2: IR spectra of 1-(2-oxoindolin-3-ylidene)thiosemicarbazide (G1)

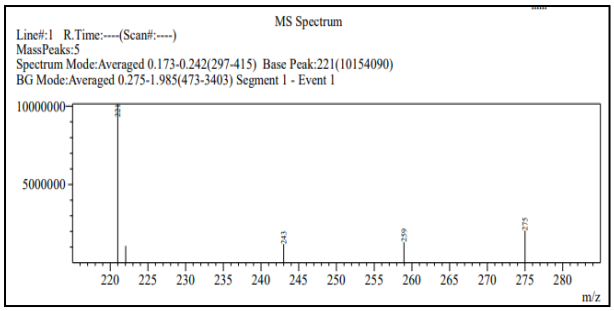

Fig. 3.1.3: Mass spectra of 1-(2-oxoindolin-3-ylidene)thiosemicarbazide (G1)

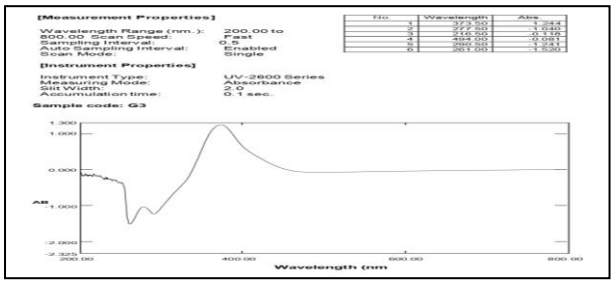

Fig. 3.1.4 : UV-Visible spectra of 1-(2-oxoindolin-3-ylidene)thiosemicarbazide (G1)

The synthesis of 1-(2-oxoindolin-3-ylidene)thiosemicarbazide (referred to as G1) was accomplished through the reaction between Isatin and thiosemicarbazide in the corresponding molar ratio. The purity of the synthesized compound was rigorously assessed via TLC analysis to ensure its integrity. Subsequent purification involved recrystallization utilizing ethanol, a step aimed at enhancing the compound's purity and crystalline structure. Comprehensive physical and analytical characterization was conducted to elucidate the compound's properties. G1 possesses a molecular formula of $C_9H_8N_4SO$, with a molecular weight of 220.253 g/mol, and exhibits a melting point of 198°C. The synthesis process resulted in a yield of 52%. Analysis via 1H NMR spectroscopy, performed in DMSO-d6, revealed characteristic peaks at δ 6.9215–7.3722 (multiplet, 3H, aromatic protons), 7.6510–7.6668 (doublet, 1H, aromatic proton), 8.6741-9.0325 (singlet, 2H, -NH2), 11.1933 (singlet, 1H, -NH), and 12.6920 (singlet, 1H, -N=NH), confirming the compound's structural attributes. Additionally, FT-IR spectroscopy unveiled peaks at 3139 cm-1 (enolic O-H), 3286 cm-1 (N-H (-NH2)), 1680 cm-1 (C=O), 1608 cm-1 (C=N), 1479 cm-1, 1460 cm-1 (C=C), 1186 cm-1 (N-H), and 1104 cm-1 (C=S), indicative of specific functional groups within G3. Mass spectrometry (m/z) exhibited a base peak at 221, further supporting the compound's identity. UV-Visible spectroscopy displayed an absorption maximum at 373 nm, adding to the compound's characterization profile. These analytical insights contribute to a comprehensive understanding of 1-(2-oxoindolin-3-ylidene)thiosemicarbazide (G1), facilitating its potential applications in various scientific domains.

3.2 Physical and spectral characterization of 3-((4 chlorobenzylidene)hydrazono)indolin-2-one (G2)

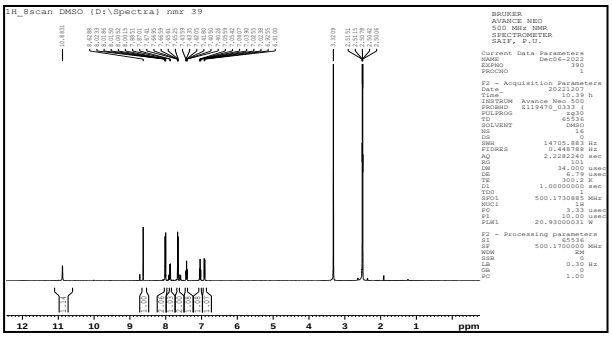

Fig. 3.2.1: 1H-NMR spectra of 3-((4-chlorobenzylidene)hydrazono)indolin-2-one (G2)

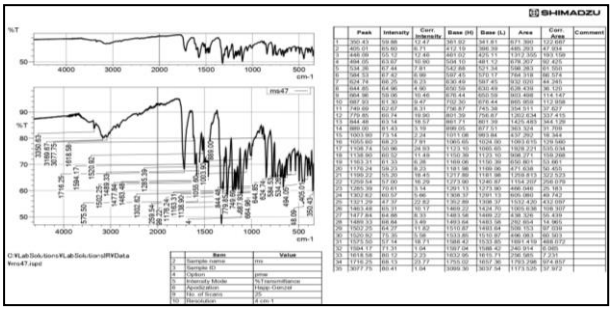

Fig. 3.2.2: IR spectra of 3-((4-chlorobenzylidene)hydrazono)indolin-2-one (G2)

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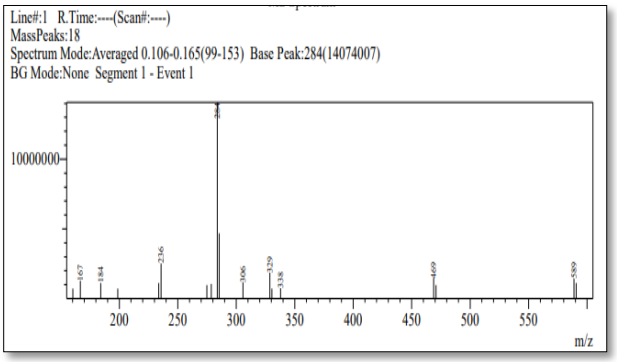

Fig. 3.2.3: Mass spectra of 3-((4-chlorobenzylidene)hydrazono)indolin-2-one (G2)

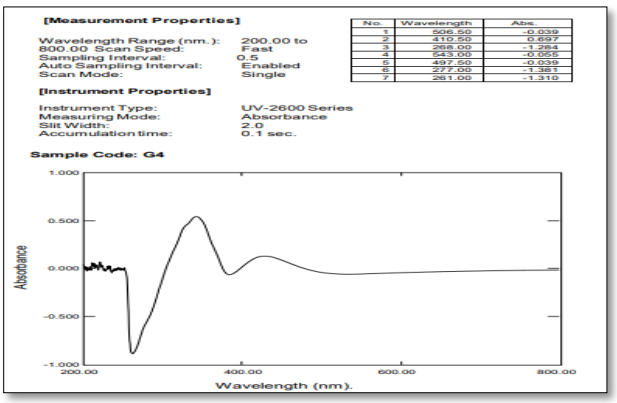

Fig. 3.2.4: Uv-Visible of 3-((4-chlorobenzylidene)hydrazono)indolin-2-one (G2)

The synthesis of 3-((4-chlorobenzylidene)hydrazono)indolin-2-one (referred to as G2) was achieved through the reaction between Isatin monohydrazone and p-chlorobenzaldehyde in the appropriate molar ratio. The compound's purity was meticulously assessed via TLC analysis to ensure its integrity, followed by recrystallization using ethanol for purification and crystalline enhancement. Comprehensive physical and analytical characterization was conducted to elucidate the compound's properties. G2 has a molecular formula of $C_{15}H_{10}N_3OCl$, with a molecular weight of 283.714 g/mol. Specific melting point data was not provided. The synthesis process resulted in a yield of 85%. Analysis via 1H NMR spectroscopy, performed in DMSO-d6, revealed distinct peaks at δ 6.9100–8.0233 (multiplet, 8H, aromatic protons), 8.6288 (singlet, 1H, =CH-), and 10.8831 (singlet, 1H, NH), confirming the compound's structural attributes. Additionally, FT-IR spectroscopy unveiled characteristic peaks at 3169 cm-1 (enolic O-H), 1618 cm-1 (C=O), 1575 cm-1 (C=N), 1489 cm-1, 1477 cm-1, 1463 cm-1 (C=C), 1285 cm-1 (=C-H), 889 cm-1, 844 cm-1, 779 cm-1, 750 cm-1 (C=C), and 644-534 cm-1 (C-Cl), indicative of specific functional groups within G3. Mass spectrometry exhibited a base peak at 284, further supporting the compound's identity. UV-Visible spectroscopy displayed an absorption maximum at 410 nm, contributing to its characterization profile. These analytical insights contribute to a comprehensive understanding of 3-((4-chlorobenzylidene)hydrazono)indolin-2-one (G2), facilitating its potential applications across various scientific disciplines.

The indole-2,3-dione based heterocyclic compounds of Schiff base (G1 and G2) were synthesized and utilized as guest molecules in the formation of inclusion complexes (IC1-IC2) with β-Cyclodextrin. Characterization of all synthesized compounds (G1-G2 and IC1-IC2) was conducted through physical and chemical analysis. Infrared spectral analysis revealed the presence of characteristic absorption bands, with aromatic (C=C) stretching observed at 1678 cm-1, N-H stretching at 3500 cm-1, aromatic C-H stretching between 1380-1465 cm-1, amide C=O stretching within 1650-1818 cm-1, C=N stretching at 1672 cm-1, and O-H stretching within 2500-3300 cm-1 [Hemmalakshmi *et al.*, (2017)]. 1H NMR spectroscopy displayed distinctive peaks for each compound (G1-G3), with G1 exhibiting signals at δ 6.89–7.12 (m, 3H,-5, 6,7), 7.21–7.39 (m, 5H- 2', 3', 4', 5',6'), 7.6608–7.6456 (d, 1H, 4), 7.7844 (s, 1H, NH), and 12.71 (s, 1H, N=NH) [Charoenchaitrakool *et al.*,(2002); Lin *et al.*, (2011)]. Mass spectrometry confirmed the predicted M+ ion of m/z, matching calculated mass values for each compound. UV-visible spectroscopy exhibited sharp peaks, with G1 and G2 displaying peaks at 373nm, and 410 nm respectively [Hemmalakshmi *et al.*, (2017)]. These comprehensive analyses provide essential insights into the structural characteristics and properties of the synthesized compounds, facilitating their further exploration in antimicrobial and antioxidant activities, as well as in the formation of inclusion complexes.

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3.3. Inclusion complex: Physical properties and Spectroscopic investigation

Table2. Physical properties of inclusion complexes (IC1 and IC2)

Sr. No.	Inclusion complex	Colour	Melting point in ºC	% Yield
1	IC1	Yellow	245°C	59
2	IC2	Orange	275°C	62

The formation of inclusion complexes is evidenced by alterations in physical properties, notably changes in melting points and the emergence of distinct colors. In the case of the compounds IC1, and IC2, the melting points of their respective inclusion complexes are recorded as, 245°C, and 275°C. Concurrently, the coloration of these complexes is observed as yellow for IC1 and orange for IC2.

3.3.1 β-Cyclodextrin:

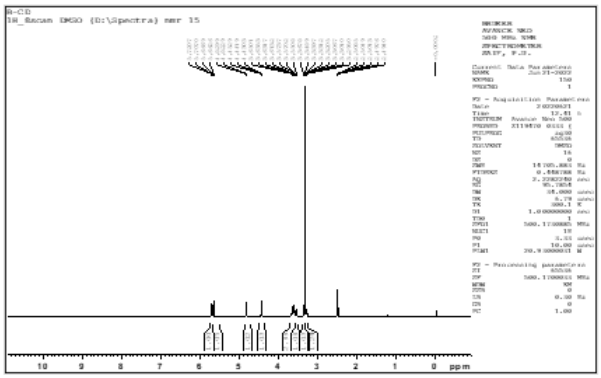

Fig. 3.3.1a NMR spectra of β-Cyclodextrin

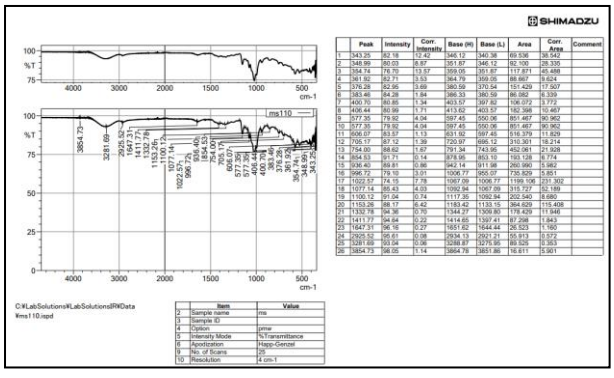

Fig. 3.3.1b IR spectra of β-Cyclodextrin

3.3.2 G1/β-CD inclusion complex (IC1)

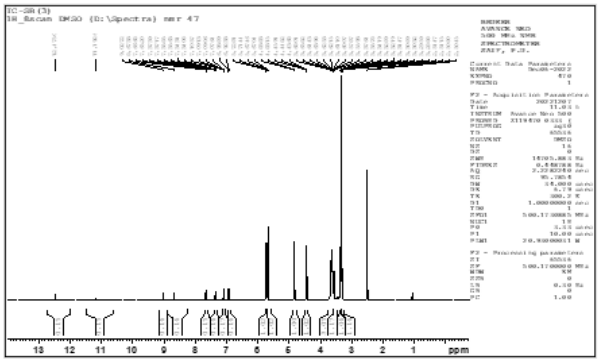

Fig. 3.3.2a 1H-NMR Spectra of G1/β-CD inclusion complex (IC1)

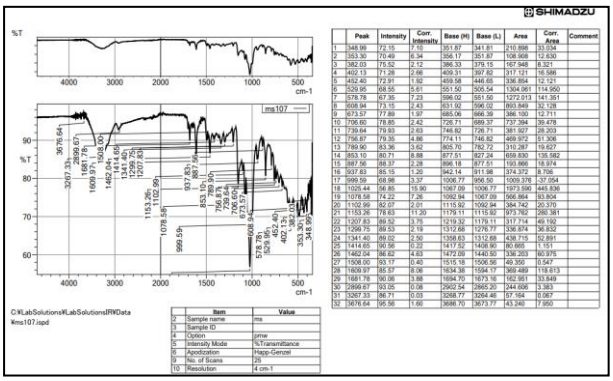

Fig. 3.3.2b IR Spectra of G1/β-CD inclusion complex (IC1)

3.3.3 G2/β-CD inclusion complex (IC2)

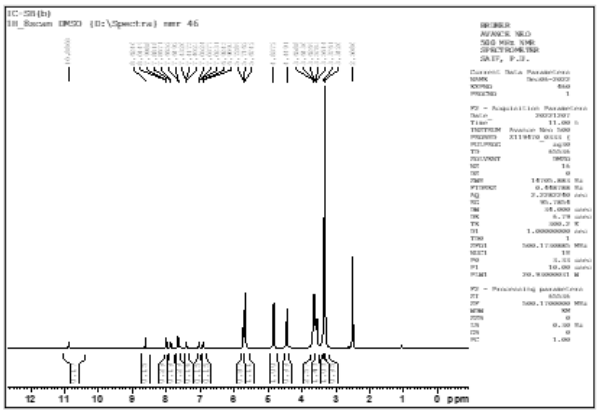

Fig. 3.3.3a 1H-NMR Spectra of G2/β-CD inclusion complex (IC2)

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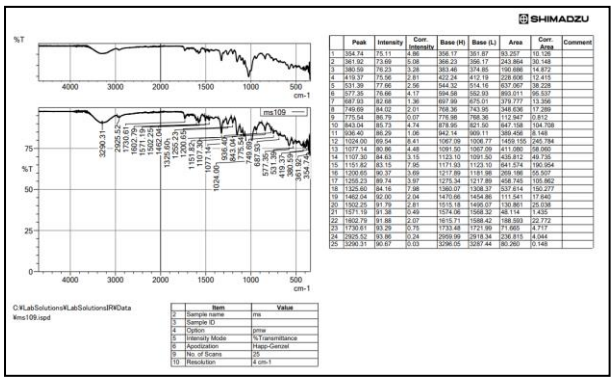

Fig. 3.3.3b IR Spectra of G2/β-CD inclusion complex (IC2)

The infrared (IR) spectrum of β -cyclodextrin (β -CD) shows peaks at 3281 cm^{-1} (O-H), 2925 cm^{-1} (C-H), and 1022 cm^{-1} (C-O-C). For the inclusion complex of compound IC1, IR frequencies appear at 3267 (N-H, NH2), (enolic O-H) disappeared, 1681 (C=O), 1609 (C=N), 1462 (C=C), 1153 (N-H), 779-739 (Ar-H), 1103 (C=S) indicating the presence of Ar-H, C=C, C=S, C=N, and C=O as expected. The IR spectra of IC2, inclusion complexes exhibit characteristic peaks corresponding to their molecular structures. Additionally, the synthesis of compounds is confirmed through their 1H nuclear magnetic resonance (NMR) data. In the 1H NMR spectra, distinctive signals are observed for different types of protons in each compound, providing further insight into their chemical composition and structural properties.

3.4 Pharmacological characterization of Isatin derivatives and their inclusion complexes.

The synthesized compounds underwent testing for antibacterial activity against Pseudomonas aeruginosa, Salmonella typhi, and Staphylococcus aureus using the Kirby-Bauer disc diffusion method (Bauer et.al., 1996). Ampicillin served as the standard drug, and both standard and test compounds were dissolved in DMSO at varying concentrations. After 24 hours of incubation at a temperature of 35-37°C, the zone of inhibition was measured and compared to the standard drug. Furthermore, antifungal activity against Candida albicans was assessed with fluconazole as the standard drug (Table 4). The zone of inhibition was evaluated after 48 hours at a temperature of 25°C. Results indicated that Isatin derivatives and their inclusion complexes (G1, G2, IC1, IC2) exhibited substantial inhibition zones at a concentration of 100mcg against the tested bacteria. All synthesized compounds displayed significant antibacterial activity. Regarding antifungal activity, Isatin compounds and their inclusion complexes demonstrated moderate efficacy against Candida albicans. Notably, IC1 exhibited the highest activity against the fungi, followed by other compounds. In summary, the study suggests that the newly synthesized compounds and their derivatives possess antibacterial activity against Pseudomonas aeruginosa, Salmonella typhi, and Staphylococcus aureus. However, further investigation is warranted to explore their pharmacological properties fully.

4. Conflicts of interests:

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript

Sample codes	Antibacterial activity (Zone of inhibition in mm)												Antifungal activity (Zone of inhibition in mm)			
	Pseudomonas aeruginosa				*Salmonella typhie*				*Staphyllococus aureus*				*Candida albicans*			
	12.5 mcg	25 mcg	50 mcg	100 mcg	12.5 mcg	25 mcg	50 mcg	100 mcg	12.5 mcg	25 mcg	50 mcg	100 mcg	12.5 mcg	25 mcg	50 mcg	100 mcg
G1	NZ	3	3	9	NZ	NZ	4	10	3	3	4	5	NZ	NZ	2	6
IC1	3	4	5	11	NZ	NZ	6	11	5	5	7	10	4	4	4	11
G2	NZ	4	6	7	NZ	NZ	3	6	NZ	NZ	NZ	7	3	3	3	4
IC2	NZ	6	8	9	NZ	NZ	3	7	2	3	4	6	5	5	6	6

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Std	7	11	14	20	8	11	13	21	8	12	16	22	12	14	18	21

Table. 4 Antimicrobial activity of Isatin derivative (Schiffs bases) and allied inclusion complexes

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